> they are present. Applicant states that hydroxyethyl cellulose and hydroxypropyl cellulose are essential to Applicants' invention. Claim 35 does not require the presence of either if sodium carboxymethylcellulose (Na CMC)is present and Sander et al disclose Na CMC. Applicant has not responded to the assertion that it would have been obvious to one having ordinary skill in the art to substitute one cellulose ether for another in view of a teaching equivalence.

Applicants respectfully traverse this rejection. The reference of record, Sander et al., does not teach or suggest Applicants' inventive subject matter as a whole as recited in the amended claims. It is not even apparent what would lead the ordinary skilled artisan to modify the Sander et al. patent disclosure to derive the subject matter claimed by Applicants.

The U.S. Supreme Court in *Graham v. John Deere Co.*, 148 U.S.P.Q. 459 (1966) held that non-obviousness was determined under § 103 by (1) determining the scope and content of the prior art; (2) ascertaining the differences between the prior art and the claims at issue; (3) resolving the level of ordinary skill in the art; and, (4) inquiring as to any objective evidence of nonobviousness.

A. The present inventive subject matter

Applicants' claims as presently amended are directed to a polymer matrix capable of holding a therapeutic drug suspended in the matrix and allowing sustained release of the therapeutic drug for prolonged periods of time. The inventive subject matter is further directed toward treating the circulatory system and muscular tissue by providing said sustained release.

Specifically, the inventive subject matter is directed to a polymer matrix consisting of negatively charged polymers and nonionic polymers combined in approximately equal amounts. This system is designed to administer effective levels of drugs for a sustained period of time. To achieve the desired sustained release, it is extremely important that there is a suitable ratio between the two polymers in the polymer matrix. (Specification, page 4, lines 9-10).

A new and unexpected aspect of the inventive subject matter is the ability to hold and release a therapeutic drug for prolonged periods of time by employing compositions with a relatively equal ratio of negatively charged polymers to nonionic polymers. It has been found that compositions with molar ratios outside the claimed boundaries develop defects, such as air pockets and separation of the polymers, inhibiting the ability of the matrix to sustain a long acting release of a therapeutic drug. (Specification, page 4, lines 13-17). It has also been unexpectedly discovered that the use of a negatively charged polymer is critical to aid in the dispersion of the drug throughout the matrix, further prolonging and controlling the release (Specification, page 4, line 18-21).

B. The prior art

In contrast, Sander et al. teach a composition for effecting bone repair which includes biocompatible particles dispersed in a matrix.

The Specification discloses a matrix which is able to form a

semisolid form. (See column 2, lines 45-47). This form is the crux of the invention for it allows a moldable gel which can be applied to the bone. The disclosed compositions are specifically designed to achieve an adequate stiffness. (See column 5, lines 18-28). To achieve the essential level of stiffness, the patent teaches a composition containing high concentrations (64% to 94% by weight) of biocompatible particles in a polymer matrix. Moreover, preferred embodiments of the invention call for increasingly higher concentrations of biocompatible particles (preferably 73% to 92% by weight, and more preferably 82% to 90% by weight) and therefore an increasingly more disproportionate polymer matrix composition. (See column 3, lines 38-47).

Sander et al. also disclose the use of a plurality of biocompatible particles suspended in the matrix. (See column 2, lines 1-13). The specification discloses that this suspension is necessary to achieve the benefits of the invention, namely a moldable, semi-solid substance for effecting bone repair with enhanced resorption.

C. The differences between the claimed subject matter and the prior art

The differences between applicants' inventive subject matter and the Sander et al. patent are startling and readily apparent from their independent and distinct disclosures and claims. In particular, applicants must employ a relatively equal ratio of negatively charged to nonionic polymers to form a matrix suitable

for a long-lasting, sustained drug release, whereas Sander et al. disclose a disproportionate polymer matrix designed to achieve enhanced stiffness, not longer, more effective, sustained drug release. Further applicants' claims are limited to specific molar ratios which exclude the suspensions of biocompatible molecules disclosed by Sanders et al.

In this regard, applicants' use of polymer matrixes are not disclosed or suggested by Sander et al. By teaching the use of increasingly disproportionate polymer matrix compositions, Sander et al. fail to appreciate the unexpected properties of using a composition containing equal mixtures of nonionic and negatively charged polymers, such as that claimed by applicants. The fact that a claimed product is within the broad field of the prior art and one might arrive at it by selecting specific items and conditions does not render the product obvious in the absence of some directions or reasons for making such selection. Ex parte Kuhn, 132 USPQ 359 (POBA 1961). Sander et al. do not recognize the advantageous properties of a polymer mixture which is not a semisolid, or the usefulness of a specific polymer mixture unexpectedly found to store and release therapeutic drugs efficiently, over prolonged periods. In failing to appreciate their advantages, Sander et al. provide no reason or incentive for using polymer matrixes as claimed by the applicants. Thus, not only does the patent fail to provide the present inventive subject matter, but because the Sander et al. patent urges the use of increasingly disproportionate polymer matrix compositions to

achieve the appropriate levels of stiffness, it teaches away from applicants' inventive subject matter.

It is also brought to the Examiner's attention that claim 1 has been amended to specifically remove sodium carboxymethylcellulose as a possible nonionic polymer. The Examiner had stated that the use of that particular molecule is anticipated by Sander et al. Therefore, Claim 1 has been added in accordance with the limitation specified by the Examiner. However, applicants maintain that the ratio and form of the claimed composition is novel and patentable, regardless of the specific choice of nonionic polymer.

The Examiner also expressed concern that the claims, as presently amended, do not exclude the biocompatible particles suspended in the matrix of the Sander et al. composition. In fact, the applicants' claims do exclude the suspensions taught by Sander et al. through the molar ratio limitation. The specified molar ratio of the claimed polymer matrix (1:0.5 to 2) provides for a relatively equally proportioned polymer mixture, and not a dis-proportionately concentrated suspension, as taught by Sander et al, and it is this equal proportion that is essential to achieve the desired properties of the claimed composition.

Further the Examiner stated that the language "consisting essentially of" is not limiting to a composition wherein the language "comprising" is present. Applicants wish to point out that their use of the transitional phrase "consisting essentially of" is limiting because it limits the components of the polymer

matrix to the group of negatively charged polymers listed in the valid Markush group and only additional immaterial elements. Such a use of transitional phrases is proper under MPEP 2173.05(h), and is not rendered improper by the presence of a valid Markush group.

Additionally, applicants point out that the Examiner's reference in the Office Action to claims 35 and 37 is misplaced because both claims have been removed from consideration in the prosecution of this patent application.

Accordingly, applicants respectfully request the Examiner to reconsider and withdraw the rejection.

It is readily apparent that there is no disclosure of facts in the prior art which support a legal conclusion that the claimed invention was obvious at the time it was made. It is a well settled principle that prior patents are references only for what they clearly disclose or suggest and that it is not proper use of a patent as a reference to modify its structure to one which the reference does not suggest.

It is readily apparent from the reference relied upon that the technology disclosed in our application is totally unrelated to that which is disclosed by this reference.

The provisions of Section 103 must be followed realistically to develop the factual background against which the Section 103 determination must be made. All of the facts must be considered and it is not realistic within the framework of Section 103 to pick and choose from any one reference only so much as will support a given position to the exclusion of other parts necessary for the

full appreciation of what such reference fairly suggests to one of ordinary skill in the art. Accordingly, withdrawal of the reference and an allowance of the claims 1, 3-5 and 7-14 is respectfully requested.

2. Rejection of Claims 1, 3-5 and 7-14 under 35 U.S.C. § 103

The Office Action states that claims 1, 3-5, and 7-21 are rejected under 35 U.S.C. § 103 as being obvious over Leshchiner et al. Applicants wish to point out that claims 15-21 have been removed from consideration and applicants will therefore view the Examiner's rejection as a rejection of claims 1, 3-5, and 7-14.

As the basis of this rejection, the Office Action states:

> Applicants argue that Leshchiner et al. disclose a two phase mixture whereas the instant claims are drawn to a single phase mixture. The claims do not recite that the mixture is single phase and in fact the polymer matrix can be suspended in the liquid medium which would be a two phase mixture.

Applicants respectfully traverse this rejection. The reference of record, Leshchiner et al., does not teach or suggest applicants' inventive subject matter as a whole as recited in the amended claims. It is not even apparent what would lead the ordinary skilled artisan to modify the Leshchiner et al. patent disclosure to derive the subject matter claimed by applicants.

The U.S. Supreme Court in *Graham v. John Deere Co.*, 148 U.S.P.Q. 459 (1966) held that non-obviousness was determined under § 103 by (1) determining the scope and content of the prior art;

(2) ascertaining the differences between the prior art and the claims at issue; (3) resolving the level of ordinary skill in the art; and, (4) inquiring as to any objective evidence of nonobviousness.

A. The present inventive subject matter

Applicants' claims as presently amended are directed to a polymer matrix capable of holding a therapeutic drug suspended in the matrix and allowing sustained release of the therapeutic drug for prolonged periods of time. The inventive subject matter is further directed toward treating the circulatory system and muscular tissue by providing said sustained release.

Specifically, the inventive subject matter is directed to a polymer matrix consisting of negatively charged polymers and nonionic polymers combined in approximately equal amounts. This system is designed to administer effective levels of drugs for a sustained period of time. To achieve the desired sustained release, it is extremely important that there is a suitable ratio between the two polymers in the polymer matrix (Specification, page 4, lines 9-10).

A new and unexpected aspect of the inventive subject matter is the ability to hold and release a therapeutic drug for prolonged periods of time by employing compositions with a relatively equal ratio of negatively charged polymers to nonionic polymers. It has been found that compositions with molar ratios outside the claimed boundaries develop defects, such as air pockets and separation of

the polymers, inhibiting the ability of the matrix to sustain a long acting release of a therapeutic drug (Specification, page 4, lines 13-17). It has also been unexpectedly discovered that the use of a negatively charged polymer is critical to aid in the dispersion of the drug throughout the matrix (Specification, page 4, line 18-21).

B. The prior art

In contrast, Leshchiner et al. teach biocompatible viscoelastic gel slurries consisting of two phases. More specifically, the slurry comprises a polymer in a liquid phase solvent, which may, or may not, be another polymer. Leshchiner et al. do not disclose any manner of achieving sustained drug release.

Leshchiner et al. teach a slurry which is able to form a suspension where the polymer does not dissolve in the liquid phase, but is uniformly dispersed (See column 2, lines 10-12). This covers a broad range of possible solvents. The solvent may or may not be a polymer, as long as it does not dissolve the polymer suspension or have an adverse reaction to living tissue. (See column 4, lines 29-60).

Leshchiner et al. also disclose the application of pressure on the gel to control the polymer concentration. (See column 6, lines 3-18). Leshchiner et al. teach that the controlling of polymer concentration in the gel phase, and hence equilibrium swelling are important functions of obtaining the desired slurry.

C. The differences between the claimed subject matter and the prior art

The differences between applicants' inventive subject matter and the Leshchiner et al. patent are startling and readily apparent from their independent and distinct disclosures and claims. In particular, applicants must employ an approximately equal ratio of negatively charged to nonionic polymers to form a polymer matrix capable of achieving sustained drug release for prolonged periods of time at effective levels, whereas the Leshchiner et al. patent discloses a polymer slurry formed to allow the suspension of a gel phase of a polymer in an aqueous phase and provides no discussion regarding sustained drug release. (See Col. 2, lines 7-11).

Leshchiner et al. teach suitable slurries of polymers suspended in an aqueous phase. Leshchiner et al. specifically teach a gel phase in a suspension, where the solvent can be any solvent that does not dissolve the polymer or effect human tissue. The applicants' claims are limited to specific molar ratios which exclude the suspensions taught by Leshchiner et al. The fact that Leshchiner et al. do not teach the effectiveness or unexpected results of any particular aqueous phase indicates their invention does not make obvious the use of a non-suspension polymer mixture calling for very specific components in very specific molar ratio ranges, as claimed by the applicants.

Perhaps the most important distinction is that Leshchiner et al. does not teach any manner of achieving sustained drug release, nor does it even disclose any properties which one reasonably

skilled in the art might think are applicable to the attainment of sustained drug release. Therefore, it would not be obvious to one of ordinary skill in the art to use the compositions disclosed by Leshchiner et al. to achieve sustained drug release where the disclosure does not teach any properties which would allow for an effective, long-acting, sustained drug release.

Further, Leshchiner et al. disclose a gel slurry where the polymer is suspended in an aqueous phase that may or may not be another polymer, whereas the applicants' inventive subject matter is specifically limited to a mixture of polymers and not a slurry (a thin watery suspension). The suspension of gel phase disclosed by Leshchiner et al. is not only absent in applicants' inventive subject matter, but would be completely inappropriate for the applicants' claimed inventive subject matter.

In this regard, applicants' use of polymer matrixes are not disclosed or suggested by Leshchiner et al. By disclosing slurries not dependent on the molar ratio of polymers, Leshchiner et al. fail to appreciate the unexpected properties of using equal mixtures of nonionic and negatively charged polymers, as claimed by applicants. The fact that a claimed product is within the broad field of the prior art and one might arrive at it by selecting specific items and conditions does not render the product obvious in the absence of some directions or reasons for making such selection. Ex parte Kuhn, 132 USPQ 359 (POBA 1961). Leshchiner et al. do not recognize the advantageous properties of a polymer mixture which is not a two phase suspension, or the usefulness of

a specific polymer mixture unexpectedly found to store and release therapeutic drugs efficiently, over prolonged periods of time. In failing to appreciate their advantages, Leshchiner et al. provide no reason or incentive for using polymer matrixes as claimed by the applicants. Thus, not only does the patent fail to provide the present inventive subject matter, but the Leshchiner et al. patent teaches away from applicants' inventive subject matter.

Accordingly, applicants respectfully request the Examiner to reconsider and withdraw this rejection.

It is readily apparent that there is no disclosure of facts in the prior art which support a legal conclusion that the claimed invention was obvious at the time it was made. It is a well settled principle that prior patents are references only for what they clearly disclose or suggest and that it is not proper use of a patent as a reference to modify its structure to one which the reference does not suggest.

It is readily apparent from the reference relied upon that the technology disclosed in our application is totally unrelated to that which is disclosed by this reference.

The provisions of Section 103 must be followed realistically to develop the factual background against which the Section 103 determination must be made. All of the facts must be considered and it is not realistic within the framework of Section 103 to pick and choose from any one reference only so much as will support a given position to the exclusion of other parts necessary for the full appreciation of what such reference fairly suggests to one of

ordinary skill in the art. Accordingly, withdrawal of the reference and an allowance of claims 1, 3-5 and 7-14 is respectfully requested.

CONCLUSION

Based upon the above remarks, the presently claimed subject matter is believed to be novel and patentably distinguishable over the prior art of record. The Examiner is therefore respectfully requested to reconsider and withdraw the rejections of remaining claims 1, 3-5 and 7-14 and allow all pending claims presented herein for reconsideration. Favorable action with an early allowance of the claims pending in this application is earnestly solicited.

The Examiner is welcomed to telephone the undersigned attorney if she has any questions or comments.

Respectfully submitted,

NATH & ASSOCIATES

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